"ANALYSIS OF PRESENTATION, MANAGEMENT AND OUTCOME FOLLOWING NEOADJUVANT THERAPY IN CARCINOMA RECTUM"

Dissertation submitted to

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY

In partial fulfillment of the requirements

for the Award of the Degree of

M.Ch BRANCH – VI

SURGICAL GASTROENTEROLOGY AND PROCTOLOGY

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY

CHENNAI

AUGUST 2014

CERTIFICATE

This is to certify that the dissertation **"Analysis of Presentation, Management and outcome following Neoadjuvant therapy in Carcinoma Rectum"** titled **submitted** by **Dr.C.Madeswaran** appearing for **M.Ch. (Surgical Gastroenterology and Proctology)** degree examination in August 2014 is a bonafide record of work done by him under our guidance and supervision in partial fulfillment of requirement of the TamilNadu Dr. M.G.R Medical University, Chennai. I forward this to the TamilNadu Dr. M.G.R Medical University, Chennai.

Prof. D. KANNAN, M.S., MCh., FRCS.
Professor
Department of Surgical Gastroenterology,
Center of Excellence for Upper GI Surgery,
Rajiv Gandhi Government General Hospital &
Madras Medical College, Chennai-3

Prof. S.M. CHANDRAMOHAN,
M.S., MCh, FACS.,
Professor and Head,
Department of Surgical Gastroenterology, Center of Excellence for Upper GI Surgery, Rajiv Gandhi Government General Hospital & Madras Medical College, Chennai-3.

Prof. R.VIMALA
DEAN
Madras Medical College,
Chennai-3.

DECLARATION

I solemnly declare that this dissertation titled "**Analysis of Presentation, Management and outcome following Neoadjuvant therapy in Carcinoma Rectum**" was prepared by me in the Department of Surgical Gastroenterology and Proctology, Centre of Excellence for Upper Gastrointestinal Surgery, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai under the guidance and supervision of **Prof.S.M.Chandramohan,** M.Ch., FACS, Professor & Head of the Department of Surgical Gastroenterology and Proctology, Centre of Excellence for Upper Gastrointestinal Surgery, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai. This dissertation is submitted to The Tamil Nadu Dr. MGR Medical University, Chennai in partial fulfillment of the university requirements for the award of the degree of M.Ch Surgical Gastroenterology and Proctology.

Place: Chennai

Date: **Dr.C.Madeswaran**

ACKNOWLEDGEMENT

I express my heartful gratitude to the Dean, **Dr.R.VIMALA MD.,** Madras Medical College & Rajiv Gandhi Govt. General Hospital, Chennai-3 for permitting me to do this study.

I gratefully acknowledge and sincerely thank **Prof. S.M.CHANDRAMOHAN M.S, M.Ch, FACS.** Professor and Head, Department of Surgical Gastroenterology and Proctology, Center of Excellence for Upper GI Surgery for his valuable suggestions, guidance, constant supervision and moral support without which this study would not have been possible.

I express my gratitude to **Prof. D. KANNAN M.S, M.Ch, FRCS,** and **Prof. G.MANOHARAN M.S,Mch,** Department of Surgical Gastroenterology and Proctology for their valuable constant supervision and moral support and guidance in doing the dissertation work.

I am extremely thankful to Assistant Professors, **Dr. A.Bennet Duraisamy, Dr. R.Prabhakaran, Dr. A.Amudhan** in the Department of Surgical Gastroenterology and Proctology for their constant support, encouragement and advice during my study.

I express my gratitude to **Prof. K. KALAISELVI** Professor and Head, Department of Medical Oncology and Prof. **SHANMUGAKUMAR S**. Professor and Head, Department of Radiation Oncology.

I also thank my past and present fellow postgraduates who helped me in carrying out my work and preparing this dissertation.

I thank **all Staff Nurses and all the Paramedical staff members** in the Department of Surgical Gastroenterology, Madras Medical College, Rajiv Gandhi Government General Hospital, Chennai for their Co-operation in conducting the study.

I thank my family members for their understanding and co-operation in completion of this work.

Last but not the least; I owe my sincere gratitude to the patients and their relatives who co-operated for this study, without whom the study could not have been possible. This work would be complete and successful if it had contributed, even in the smallest possible way to alleviate their suffering.

INDEX

Sl.NO	CONTENTS	PAGE
1	Introduction	
2	Rationale for the Study	
3	Aim of the Study	
4	Review of Literature	
5	Materials and Methods	
6	Results	
7	Discussion	
8	Conclusion	
9	Bibliography	
10	Appendix	
	Case Record Form	
	Consent Forms	
	Master Chart	
	Ethical Committee approval	
	Plagiarism and visual receipt	

Analysis of Presentation, Management and outcome following Neoadjuvant therapy in Carcinoma Rectum

BACKGROUND:

The potential for curative resection is the most important component of multimodality treatment of Rectal cancer. In locally advanced Rectal cancer lymph node involvement and positive circumferential resection margin are common which leads to local recurrence and metastatic disease. Postoperative chemo Radiotherapy significantly improves local recurrence control and improved overall survival. Several studies have shown that Preoperative Chemo Radiotherapy has increased local control rates, tumor down staging, sphincter saving procedures and enhancing resectability

AIM:

The aim of the study is to analyze the surgical outcome following neoadjuvant Chemo Radiotherapy in patients with locally advanced operable Rectal cancer (T3, T4 and Node positive tumor). To analyze whether preoperative Chemo Radiotherapy is beneficial to the patient or not, Analyzing the primary end points and analyzing Secondary endpoints.

MATERIALS & METHODS

This retrospective study was conducted in the Department of Surgical Gastroenterology, Rajiv Gandhi Government General Hospital, Madras Medical college, Chennai. From March 2012 to February 2014. The study was approved by the medical ethics committee of the hospital.

15 patients with advanced carcinoma rectum were included in the study.

Eligibility Criteria

- All patients with locally advanced operable rectal cancer i.e. T3, T 4, node positive tumors without distant metastasis,Patients with histologically confirmed adenocarcinoma within 12 cm from anal verge(locally advanced Rectal carcinoma in Middle and Lower third of Rectum),Patients with Carcinoma Lower third Rectum with upper Anal canal involvement, Radiological evidence of mesorectal invasion
- **Exclusion Criteria**- Patients who previously had cancer other than basal

cell carcinoma of skin, Patients who had received chemotherapy or radiotherapy, Patients with contraindications to chemoradiotherapy, Distant metastasis, Patients with poor performance status

Preoperative evaluation- Loco regional staging was done with contrast enhanced CT of abdomen and pelvis, Endorectal ultrasound and cystoscopy in cases suspected of bladder invasion.. Distant metastasis was excluded by contrast enhanced CT of abdomen and pelvis, chest X-ray and if necessary a CT chest. Colonoscopy was done to rule out synchronous lesions. A basic work up including complete hemogram, Renal function tests, Liver function tests, Tumor markers –CEA, Pulmonary function tests and Cardiac tests – ECG &Echocardiogram was done to rule out any major illness and to confirm the patient's fitness for surgery. **Treatment** Preoperative external beam radiotherapy was given for a total dose of 50.4 Gy in 28 fractions of 180 cGy each, five times per week for total duration of five and a half weeks.. The radiotherapy was given to include the tumor area and its drainage lymph nodes.

RESULTS

Neoadjuvant chemo radiotherapy helps significant downsizing and downstaging of tumor as it causes tumor shrinkage. In this study downsizing occurred. This is almost in accordance with other studies which have shown similar significant regression of the tumor after chemoradiotherapy.

Among fifteen patients Fourteen patients underwent surgery at six weeks after chemoradiotherapy; one patient had surgery after seven weeks in post chemoradiotherapy period. Five patients underwent anterior resection. Ten patients underwent abdominoperineal resection. Of the twelve patients who had been treated for locally advanced carcinoma Rectum for whom APER was planned, a sphincter conservation surgery was possible in two of them after neoadjuvant chemoradiotherapy and those patients underwent anterior resection. Before neoadjuvant chemoradiotherapy only three anterior resections were planned. After it, five anterior resections were done with covering ileostomy done to protect the anastomosis as well as to reduce leak related complications

CONCLUSION

Neoadjuvant chemoradiotherapy given in operable locally advanced mid

and low rectal cancers causes significant downsizing, downstaging of the tumour, increases the rate of sphincter conservation surgeries. The toxicity of chemoradiotherapy is minimal, patient compliance is good. The postoperative complications are not increased and it helps decrease the incidence of local recurrence .The effect on survival has to be determined on long term follow up only. Hence it is beneficial to administer it to patients with locally advanced operable mid and low rectal cancers.

INTRODUCTION

Multimodality treatment is the most important component of potential for curative resection of Rectal cancer. Local recurrence and metastatic disease in locally advanced Rectal cancer are due to positive circumferential resection margin and lymph node involvement. Overall survival and local recurrence control are improved by Postoperative chemo Radiotherapy. Preoperative Chemo Radiotherapy has increased local control rates, tumor down staging, sphincter saving procedures and enhancing resectability a fact shown by several studies. This study on Neoadjuvant Chemoradiotherapy for carcinoma Rectum evaluates presentation, potential benefits and outcome following multimodality treatment for locally advanced operable Rectal cancer.

RATIONALE FOR THE STUDY

Trials comparing different treatment modalities for carcinoma Rectum have arrived at different conclusions. This study is to analyze of Presentation, Management and outcome following Neoadjuvant therapy in Carcinoma Rectum" in our super specialty department, hence to formulate a standard method in locally advanced Rectal cancer for patient selection, type of anastomosis and perioperative care to achieve good outcome after neoadjuvant therapy.

AIM OF THE STUDY

The aim of the study is to analyze the surgical outcome following neoadjuvant Chemo Radiotherapy in patients with locally advanced operable rectal cancer (T3, T4 and Node positive tumor).

The main aim is to analyze whether preoperative Chemo Radiotherapy is

1) Beneficial to the patient or not.

2) Analyzing the primary end points- are downsizing of tumor, down staging of the tumor, sphincter preserving rates, Toxicity of Chemo Radiotherapy regimen and compliance for the regimen

3) Analyzing Secondary endpoints- which are analyzed in other trials are the incidence of local recurrence, distant metastases. The incidence of peroperative complications and postoperative complications also analyzed.

REVIEW OF LITERATURE

Colorectal cancer accounts for about a third of all colorectal malignancies and second commonest cause of cancer death. Many of the locally advanced cancer Rectum are unresectable at time of presentation. Lack of appreciable improvements in the past decades made many clinicians and investigators to look for other better and effective different therapeutic modalities in addition to surgery In 1970s several clinicians reported favorable and conflicting results on this. Results revealed that chemotherapy in addition to Radiotherapy had place in the management of potentially operable rectal cancer.

In 1969 Moertel and Reitemeier showed that ChemoRadiotherapy (external beam RT and 5FU) resulted in a significantly better subjective as well as objective results in the treatment of stage ii/ iii gastrointestinal malignancies.

Incidence of sporadic colorectal cancer increases significantly above 45 or 50 years of all age groups, making age a factor in colorectal carcinoma. Lack of physical activity with obesity and Ingestion of high fat and high red-meat, leads to increased incidence and mortality rates observed in etiology of Rectal cancer.

ANATOMY OF RECTUM

- Rectum is 12 to 15 cm in length, located in pelvis
- Lacks taeniaecoli or epiploic appendices
- occupies the curve of the sacrum in the true pelvis
- Anterior surface is partly intraperitoneal and posterior surface and mesorectum are almost completely extra peritoneal
- Rectum has three curves, -*valves of Houston*. The middle valve folds to the left
- The endopelvic fascia lines the walls and floor of the pelvis.
- Fascia propria is a thin condensation of the endopelvic fascia that forms an envelope around the mesorectum Waldeyer's fascia posterior fascia, connecting the presacral fascia to the fascia propria at the level of S4
- Sympathetic supply of Rectum from the preganglionic lumbar splanchnic L1 to L3, synapse in the Preaortic plexus, postganglionic elements follow the branches of the IMA
- Pelvic plexus is adherent to the pelvic sidewalls and is adjacent to the lateral stalks

- Parasymphathetics from S 2,3,4
- Dissection between the fascia propria and presacral fascia follows the principles of surgical oncology
- Blood supply from Inferior mesenteric artery, Internal iliac artery
- Venous drainage into inferior mesenteric vein and to iliac veins
- Lymphatics and lymph nodes and vessels located in retroperitoneum.

MODE OF SPREAD OF RECTAL CANCER

Carcinoma Rectum spreads through various routes –

- Direct
- Lymphatic,
- Venous
- Transcoelomic
- Implantation

Direct spread of tumor can result in proximal, distal, in longitudinal and transverse directions. In 1983 Williams et al revealed that distal

intramural spread greater than 1 cm is uncommon. There is no evidence to show a distal margin of 5cms in the resected specimen improves survival by decreasing recurrence.

Radial spread from posterior wall of Rectum involve Waldayer's fascia through mesorectal involvement. Tumors in Anterior wall of Rectum in males below the level of peritoneal reflection may involve Prostate, Seminal vesicle or Urinary bladder. William et al endorsed that leaving residual tumor tissue in the pelvis is the cause for local recurrence.

LYMPHATIC SPREAD

Rectal malignancies can spread in upward, downward and radial directions. Discontinuous spread occurs in 30% cases. Extensive lateral spread occurs in extra peritoneal tumors and it is uncommon in tumors above peritoneal reflection.

Nodes involved in rectal malignancy are Mesorectal nodes, Iliac nodes and anal canal involvement results in enlargement of inguinal nodes.

Blood spread can occur to Liver, Lung, Kidneys, Bones and ovaries. Prognosis is worse in venous invasion.

Extramural and intra mural veins of the Rectum can be involved in advanced malignancies and worse prognosis is in extramural vein involvement.

LOCAL RECURRENCE IN RECTAL CANCER

ROLE OF TOTAL MESORECTAL EXCISION

Total MesoRectal excision is precise sharp dissection around the integral mesentery of Rectum. Lymph nodes, loose areolar tissue and blood vessels in mesorectum harboring subclinical micro metastatic tissue are removed enbloc with tumor bearing Rectum with adequate oncological clearance.

Total MesoRectal Excision was introduced by Heald in 1982.[2]

Arbman[3] et al in 1996 compared their results before and after adapting Total Mesorectal excision techniques. TME resulted in significant reduction of local recurrence and increase in survival.

Tumors of middle and lower third of Rectum need Total MesoRectal excision. In case of upper rectal tumors mesorectal excision should be done 5cms below the lower border of the tumor, which may cause ischemia of the Anorectal stump and likely to result in anastomotic leak, which needs covering stoma in patients undergoing TME. TME has

reduced local recurrence rates and improved survival, sharp dissection performed in the areolar tissue behind the mesentery, in front of the sacrum and at the level of Waldeyer fascia. Fascia propria should be intact with proper rectal dissection; total mesorectal excision is done for cancers of the distal rectum for which APR or low anterior resection and coloanal anastomosis.

More proximal rectal cancers, use a margin of approximately 4 cm of distal mesorectum because tumor deposits in the mesorectum are rarely reported 4 cm beyond the tumor

ROLE OF LATERAL PELVIC LYMPHNODE DISSECTION(34)

Rectal cancers tumor spreads laterally to obturator, hypogastric and nodes along iliac vessels and upwards along superior rectal and inferior mesenteric vessels.

Positive mesorectal nodes associated with high local recurrence rate. Extended resection results in poor quality of life as the pelvic autonomic nerves are sacrificed during lateral lymph node dissection.

Autonomic nerve preservation procedures were developed resulting in improved urinary function. Morita[5] et al in 2003 has shown that overall recurrence-rate was only 6.3 % and five year survival was 47 %. after

lateral lymph node dissection, the prognosis of patients with pelvic autonomic plexus involvement was unfavorable.

Outcome between adjuvant chemoradiotherapy and lateral pelvic lymph node dissection following total mesorectal excision for middle rectal tumors is studied by Jin C Kim et al[6] No difference in disease free survival(67.3% vs 68.6 %).*or* overall survival (78 % vs 73.9%) Loco regional recurrence rate was 2.2 fold higher in lateral lymph node dissection group (16.7 % vs7.5 5 ,p = 0.044).

Addition of lateral lymph node dissection to total mesorectal excision prolonged operative time and increased the transfusion, concluded that even after lateral lymph node dissection, postoperative chemoradiotherapy needed to decrease local recurrence.

High incidence of loco regional and distal recurrence in locally advanced rectal cancers noted following surgical treatment. Other neoadjuvant and adjuvant Treatment modalities tried to improve results.

Patients with rectal cancer can be divided into three main groups. Most are resectable cancers, borderline resectable disease, (breached circumferential margins as predicted by imaging studies.), fixed unresectable cancers.

Unresectable group – ends in leaving tumor within the pelvis,after chemoradiotherapy turn resectable. Residual microscopic disease can persist after surgery at resection margins, within lymph nodes, or in distant metastatic sites in resectable cancers. The incidence of micro metastases in lymph nodes T1 -12%, T2-22% and T3,T4-58% .In locally advanced rectal cancer lymph node involvement and positive resection margin leading to local recurrence and metastatic disease. To improve local control and overall survival (OS) chemotherapy and radiotherapy used as adjuvant therapy to eradicate cells at the margins or in discontinuous areas of tumor within the pelvis, in nodes, or in distant metastatic sites. High risk for local recurrence and poor survival reported with preoperative radiotherapy alone in borderline unresectable cancers, which emphasizes the need for combining trimodality therapy .Chemotherapy as a component of chemoradiotherapy, act as a radio sensitizing agent and eradicate distant micro metastases and it is investigated with different agents in a number of trials.

CHEMOTHERAPEUTIC DRUGS

Fluropyrimidines

5-FU - an inactive drug, converted to 5-fluorouridine-5′-triphosphate (FUTP), by serial reactions and then incorporated into RNA, where it interferes with RNA processing and mRNA translation.

5-FU, resulting in inhibition of DNA synthesis and function.

5-FU is administered intravenously& clinical activity of this drug is highly schedule-dependent. It has short half-life, on the order of 10–15 minutes, infusional schedules favored over bolus schedules.

Toxicity

Myelosuppression

Diarrhea

Nausea and vomiting

Neurotoxicity

Skin toxicity by the hand-foot syndrome.

CAPECITABINE

- a fluoropyrimidine carbamate prodrug with 70–80% oral bioavailability
- converted to its active form in tumor
- side effects Diarrhea and the hand-foot syndrome myelosuppression, nausea and vomiting, and mucositis-less than infusional 5FU

PLATINUM ANALOGS

Cisplatin

- kills tumor cells in all stages of cell cycle and bind DNA leading to inhibition of DNA synthesis and function.
- bind to both cytoplasmic and nuclear proteins, contribute to their cytotoxic and antitumor effects
- Platinum complexes appear to synergize with other anticancer drugs-5FU
- extensively cleared by the kidneys and excreted in the urine, needs dose modification in renal dysfunction
- **Oxaliplatin** –preferred as first line drug with 5FU and Folic acid
- Toxicity is reversible neurotoxicity.

Role of preoperative radiotherapy

On administering preoperative radiotherapy the size of primary tumor and the number of nodes involved are reduced. The extent of pathological down grading of tumor achieved varies with the dose of radiation used, proved by MRC[32] trial in 1984, significant reduction of 30 % of number of nodes involved and negative nodes after a fractionated

irradiation of 20 Gy, but no difference was observed between control group and which received a single dose of 5 Gy. Preoperative radiotherapy also reduces local recurrence. It helps in reducing the size and extent of local spread and makes locally advanced tumors operable, associated with high toxicity and delay in abdominal and perineal wound healing.

No improvement in overall survival compared to surgery alone. Aim of extensive study in Preoperative radiotherapy was improving local control

In 1974 Steams.et al[7] reported on the results in the trial of preoperative radiotherapy, in Memorial Sloan Kettering Cancer Centre in New York. Patients were randomized to receive 20 Gy of preoperative radiotherapy or surgery only. No improvement in local recurrence or overall survival was noted.

The Veterans administration Oncology Group (VASOG) had 20 Gy given preoperatively for two weeks followed by surgery. Additional 5 Gy if tumor was within five cm of anal verge. There was reduction in number of nodes involved after irradiation and down grading of the tumor. Reduction in local recurrence after radiotherapy noted.

Swedish Rectal cancer group[27] -short course of radiotherapy studied extensively. 25GyRT over 5 days in 5 fractions followed by surgery in 7 days improved overall survival and decreased local recurrence

- Follow-up (13 years) - hypo fractionated radiotherapy resulted in improved overall survival-from 30%- 38% with short course therapy
- Improved local recurrence rate from 26%to 9%.Cancer specific survival from 62%-to 72%

Role of Radiotherapy in unresectable Rectal cancer

If CT shows unresectable tumor, preoperative radiotherapy in combination with chemotherapy or alone is recommended. Preoperative radiotherapy for locally advanced tumors using doses of 45-50 Gy is capable of down staging without chemotherapy. The 5-year survival rate was only 18% after complete resection, and these patients continued to have local failure.

Patients have even poorer overall median survival duration of 8-10 months who remain unresectable after radiotherapy

Unresectable Rectal Cancer

Randomized Trials of Chemoradiotherapy versus Radiotherapy. In a single small phase III randomized study, fixed inoperable rectal cancer in 70 patients were treated. Chemoradiotherapy delivered methotrexate, 5-fluorouracil and folinic acid in combination with hyperfractionated split-course to total dose of 40 Gy over 8 weeks. The trial showed an advantage in terms of local control and resectability for the chemoradiotherapy arm.

5-year survival rates were 18% versus 29% (nonsignificant) for radiotherapy versus chemoradiotherapy. Local recurrence-free survival rates at 5 years - 35% versus 66% (p.03). These data support the view that chemoradiotherapy is more effective than radiotherapy. For patients with T1N0 or T2N0 rectal cancer intensification of the chemoradiotherapy component achieves a higher pathological complete response, without a longer overall survival. The risk for metastatic disease predominates and very low levels of local recurrence are achieved in this group of patients.

Facilitating Sphincter-Sparing Procedures

Bulky anterior tumors in obese men and low rectal cancers (3-6 cm from the anal verge) with a narrow pelvis has technical difficulty in surgery if sphincter-sparing surgery is the aim . Tumor shrinkage back from the distal margin and further sphincter-sparing surgery is achieved by

long course chemoradiotherapy followed by a planned delay prior to surgery.

Phase II studies with chemoradiotherapy showed impressive results and an excellent outcome if marked shrinkage of the distal tumor margin is seen on long term follow-up 10% [11] or even a 20%[12] higher chance of overall sphincter-sparing surgery achieved, which is shown in Subset analysis of randomized trials with preoperative CRT (10).

Sphincter-sparing surgery depends on many factors experience:

Accessibility, Tumor size, Location surgical training and the individual's philosophy regarding risk and experience.

A randomized trial with short course radiotherapy against preoperative chemoradiotherapy with the endpoint of sphincter-sparing surgery showed no difference[13], surgeons (Polish Colorectal Study Group) tested neoadjuvant chemo radiation to short-course preoperative radiation (25 Gy in five fractions) in resectable clinically staged T3 and T4 tumors, To chemoradiation -5040 cGy at 180 cGy per fraction with chemotherapy (5-FU 325 mg/m2/day and leucovorin 20 mg/m2/day given as rapid infusion on 5 consecutive days during weeks 1 and 5 of radiotherapy)

Adjuvant chemotherapy was optional. Acute toxicity and local recurrence were high in chemoradiation arm (18.2Vs3.2 & 9%Vs 14.2%). No significant difference in, disease free survival, overall survival or late toxicity.

Preoperative chemoradiotherapy versus Postoperative chemoradiotherapy in Resectable Rectal Cancer

A randomized trial compares postoperative chemoradiotherapy with preoperative chemoradiotherapy.

Three trials in this setting - the National Surgical Adjuvant Breast and Bowel Project (NSABP) R03, German CAO/ARO/AIO-94 trial the intergroup trial INT-0147

National Surgical Adjuvant Breast and Bowel Project Protocol R-03[14]

To determine preoperative chemotherapy and radiation therapy in the management of operable rectal cancer. Patients with primary operable rectal cancer were randomized to multimodality therapy after curative surgery or preoperatively. All patients received seven cycles of 5-fluorouracil (FU)/ leucovorin (LV) chemotherapy. The preoperative arm (Group 1) received the first three cycles of chemotherapy and all radiation therapy (5,040 cGy) before surgery, and four cycles of chemotherapy post

operatively. The postoperative arm (Group 2) received all chemotherapy and radiation after surgery. 5- Fluorouracil and leucovorin chemotherapy was given during the first and fifth week of radiation therapy. Primary study end points - overall survival and disease-free survival. Secondary end points included tumor down staging, primary tumor response to combination therapy, local recurrence and sphincter preservation.

Overall treatment-related toxicity was similar in both groups. No patient was inoperable due to progressive local disease. In both groups use of protective colostomy in patients undergoing sphincter-sparing surgery and perioperative complications in surgical patients were similar. Evidence of tumor down staging in evaluable patients undergoing preoperative therapy, with 8 % of Group 1 patients had a pathologic complete response.

Preoperative chemotherapy and radiation therapy regimen used were tolerable and safe as standard postoperative treatment, a trend to sphincter preservation and tumor down staging in the preoperative arm. This trial was closed prematurely due to poor accrual. In Preoperative chemoradiation group statistically significant improvements in disease free survival at 5 years (64.7%---53.4%) and better overall survival at 5 years (74.5%---65.6%).

NSABP-R-04 trial-[14]

Primary end point- local tumor control. It compared preoperative use of infusional 5FU with or without Oxaliplatin to Capacitabine with or without Oxaliplatin.

No difference in complete pathological response, sphincter preservation or overall staging. Toxicity is more with Oxaliplatin containing regimes and addition of oxaliplatin did not improve clinical outcomes.

Phase III trial Capacitabine Vs 5FU

Chemoradiation in neoadjuvant arm showed significant difference 3 year survival in Capacitabine arm(75.2% Vs 66.6%) and 5 year overall survival 75.7% for capacitabine arm,66.6% for 5FUarm, which supports the use of capacitabine with radiation therapy.

Intergroup trial INT-0147

After randomizing only 53 patients, Intergroup INT-0147 trial closed early because of poor accrual.

The planned RT dose was 50.4 Gy.

The German CAO/ARO/AIO-94 Trial (12,24)

The German CAO/ARO/AIO-94 study 1995, for stage II/III resectable rectal cancer. To investigate preoperative 5-FU-based chemoradiotherapy versus postoperative combined- modality treatment The primary endpoints were disease free survival, overall survival, and loco regional and distant control. The secondary endpoints included the rates of curative (R0) resections, toxicity, sphincter- sparing surgery and surgical complications. [12]

Preoperative chemoradiation with 5040 cGy in 28 fractions along with PVI 5-FU (1000 mg/m2/day over 120 hours during weeks 1 and 5 of radiation) and postoperative chemotherapy (four 5-day cycles of 5-FU) or postoperative chemoradiation that differed only by the addition of another 540-cGy boost. Total mesorectal excision (TME) was performed either within 6 weeks after preoperative treatment or was followed by adjuvant treatment 1 month postoperatively. The primary outcome of OS did not differ significantly at 5 years -preoperative (76%) and postoperative (74%) groups. Local recurrence improved to 6% compared to 13% at 5 years (P = 0.006). Preoperative delivery improved the rate of any acute grade 3 or 4 toxicity from 40% to 27% (P = 0.001) & late toxicity from 24% to 14% (P = 0.01) 39% in the preoperative group –underwent a sphincter-preserving approach, versus 19% in the postoperative group (P = 0.004).

Preoperative approach is the preferred method because of improved local control, better toxicity profile and improved sphincter preservation for low-lying tumors. The locoregional failure rate was 13% for the postoperative arm.

Preoperative chemoradiotherapy -6%, Overall survival rate and Disease free survival was greater in the preoperative arm. for those patients, initially felt to have abdominoperineal excision slightly higher sphincter-sparing surgery rate was noted. In addition, compliance 9 2 % in the preoperative arm and was low for the postoperative arm, and only 54% received the full radiotherapy dose.

Acute and late toxicities - less frequent in the preoperative arm, Patients in the postoperative arm would have received a 10% higher radiotherapy dose (5.4-Gy radiation boost in the postoperative arm). Because of the constraints of acute and late toxicities Radiotherapy dose escalation has rarely been evaluated in rectal cancer.

The **Lyon R 96-02**[16] **study** used contact therapy with an extra 8.5 Gy in three fractions to boost external beam radiotherapy. Higher complete clinical response rate and a higher sphincter-sparing surgery rate are seen. No difference in overall survival or loco regional failure or overall survival at 2 years , even with Dose escalation prior to surgical

resection which is illogical to improve local control. If surgery can achieve a good quality mesorectal excision, then recurrences are likely to lie outside. Higher rate of acute toxicity seen with dose escalation of radiotherapy.

In 1984, the EORTC study -two-arm randomized clinical trial to compare the efficiency of radiotherapy alone before radical surgery with preoperative administration of radiotherapy with 5- fluorouracil .(247 patients)Total tumor dose of 34.5 Gy in 15 fractions of 2.3 Gy each (over an overall period of 18 days)'. Patients receiving combined preoperative therapy had intravenous 5-FU injection in the dose of 10 mg per kg of body weight (375 mg/m^2) during the first four days 4 to 6 hours prior to irradiation. Surgery usually followed within 2 weeks after the last irradiation.

The trial established an advantage in terms of local control and resectability for the chemoradiotherapy arm - a marginal statistical significance of P=0.06. Combined modality arm had a higher postoperative death and incidence of side effects it had a greater effect in controlling the disease process, mainly distant metastases to the liver. No difference was observed in local recurrence. Though not statistically significant Disease free survival was longer in the combined modality group.

The incidence of deaths due to malignancy was higher in the radiotherapy alone group. And nonmalignant and intercurrent deaths were higher in the combined modality group. The authors concluded that side effects and intercurrent deaths can be effectively reduced by observing with adjuvant therapy and more stringent selection in disease and patients' criteria,

EORTC 22921 Trial [17,18]

In 1993 The EORTC 22921 trial was enrolled 1,011 patients with T3/T4 resectable rectal cancer

With endpoints of disease free survival and overall survival

Patients were allocated to the following four arms:

Arm 1, preoperative radiotherapy 45 Gy in 5 weeks;

Arm 2, preoperative radiotherapy plus two 5-day chemotherapy courses (fluorouracil 350 mg/m2 /d and leucovorin 20 mg/m2 /d) in the first and fifth week of radiotherapy;

Arm 3, preoperative radiotherapy plus four postop chemotherapy courses and Arm 4, preoperative radiotherapy and chemotherapy plus postoperative chemotherapy.

Role of the duration and timing

Of 5-FU-based chemotherapy both in combination with preoperative radiation therapy, and in the postoperative adjuvant setting are tested. The trial stratified according to T stage, distance to the anal verge, sex.

Total mesorectal excision (TME) was only recommended in 1999. (2)

Compliance with the preoperative chemotherapy was high, only 42.9% adhered to the postoperative component of chemotherapy. The addition of preoperative chemotherapy to radiotherapy caused significant downsizing ($p< 0.001$), down staging ($p < 0.001$), smaller number of examined lymph nodes, less frequent lymph vascular invasions[18]. Toxicity was higher in the chemoradiotherapy arm.

Complete pathological response rate was higher in the chemoradiotherapy arm and higher sphincter-sparing surgery rate was offered only a marginal benefit (55.6 % versus52.4%; p .05). At 5 years the loco regional failure rates were 17% with radiotherapy and 8% with chemoradiotherapy.

65.2% is the 5 year survival rate for both groups and no significant difference seen in disease free survival or overall survival between groups.

A major conclusion of the study 5FU based chemotherapy when combining with radiotherapy confers advantage in local control

Federation de Francophone de Cancerologie Digestive -FFCD 9203 Trial[19]

733 patients were randomized in the FFCD 9203 trial[19] with T3/T4 resectable rectal cancer, between pre-operative radiotherapy and preoperative chemoradiotherapy to a dose of 45 Gy. The same chemotherapy regimen (5-FU, 350 mg/m^2, and folinic acid). overall survival was the primary endpoint. Patients received postoperative adjuvant chemotherapy and compliance was70% **Compliance** in the preoperative chemoradiotherapy arm was 93%.

The rate of grade 3 or 4 acute toxicity higher in the chemotherapy arm (14.6%, versus 2.7% for radiotherapy alone; p<.05). Complete sterilization of the operative specimen more in chemoradiotherapy(11.4% *v* 3.6%; *P* <.05)

5year local recurrence is low in combined modality group (8.1% Vs 16.5% P<.05). Overall survival, Sphincter preservation and surgical complications were similar in two arms.

A similar number of patients in each arm developed metastatic disease (99 following radiotherapy and 107 following chemoradiotherapy). Treatment with TME reduced the local recurrence rate to 14% for radiotherapy alone and 5% for chemoradiotherapy from 1999

The Polish Trial [13,30,35]

316 patients randomized between preoperative conventional chemoradiotherapy (50.4Gy in 28 daily fractions with 5-FU and folinic acid and short course preoperative radiotherapy.

Aim - Evaluation of sphincter-sparing surgery in short course five fractions of radiotherapy and immediate surgery with long course chemoradiotherapy with an interval. The main endpoint was Sphincter-sparing surgery. Long fractionation chemoradiotherapy regimen has been directly compared with short course preoperative radiotherapy for the first time. Complete pathological response rate was1% in the short course preoperative radiotherapy arm, 15% in the chemoradiotherapy arm. No impact on sphincter preservation 61% in the short course preoperative radiotherapy versus 58% in the chemoradiotherapy (p=0.57).

A circumferential resection margin of 1 mm was observed in13% after short course preoperative radiotherapy and 4% after chemoradiotherapy .

Local failure rate 14.2% in the chemo radiotherapy versus 9% after short course preoperative radiotherapy

No difference seen in overall survival and disease free survival

In the recent European randomized trials to neoadjuvant radiotherapy addition of 5-FU based chemotherapy led to overall survival

- Tumor down staging Significantly better
- Pathological complete response
- Better local control
- No Longer- overall survival, disease free survival, and a higher chance of sphincter preservation
- Significant problem remains with metastatic disease.

Adding a second drug (mitomycinC, oxaliplatin, or irinotecan) results in a higher pathological complete response rate, and more effective in killing micro metastases, but longer disease free survival and overall survival is not demonstrated.

Dutch Colorectal Cancer Group. Kapiteijn etal [24]

Short term RT (25Gy in 5 fractions) with TME Vs short term RT (25Gy in 5 fractions)

- At 2 years in both arms overall survival was 82%,
- Radiation improved the local failure rate at 2 years for patients in macroscopic tumor removal from 8.2% to 2.4% (*P* = 0.01).
- Long term follow-up(12 years) showed 10 –year survival improved in Stage iii CRM negative receiving surgery and RT(50%) than surgery only (40%--P.032)

Oxaliplatin added trials- STAR-01, NSABP R-04, ACCORD12 and CAO/ARO/AIO-04.

STAR-01 [52] **-** primary end point – overall survival (infusional 5FU/RT - With / Without Oxaliplatin) toxicities of grade ¾ are more in oxaliplatin arm (24%Vs 8% P<.001)

NSABP R-04 trial -primary end point is local tumor control complications are common after Oxaliplatin addition. CAO/ARO/AIO-04 [53] initial reports revealed significant complete pathological response (17% Vs13% P =.038%) rates in oxaliplatin arm due dose variation of 5FU regimes

CAPACITABINE /RT- with/without OXALIPLATIN TRIAL-

ACCORD12 /0405 Prodige 2 Trial [54] – Primary end point pathologic complete response, Toxicities are more with oxaliplatin arm25%Vs 11%,

Complete pathological response 19.2% in oxaliplatin added arm Vs 13.9, Minimal residual disease -39.4 % in Oxaliplatin arm Vs 28.9%. In neoadjuvant chemoradiation - addition of oxaliplatin not recommended.

ARISTOTLE TRIAL[55]

A phase III randomized trial in MRI defined locally advanced rectal cancer, using Standard Vs Novel chemo radiotherapy as preoperative treatment.

Aim- improves outcome after addition of second drug to chemotherapy regimen

UK based multicenter, prospective, double arm study with disease free survival as primary end point & secondary end point-disease specific survival, overall survival, loco regional failure, CRM margins, histopathological complete tumor response, surgical morbidity, quality of life, tumor cell density.

Study using addition of Irinotecan to standard Capacitabine based regimen, ARM-A-Capacitabine 900mg twice daily for 5 days weekly for 5 weeks along with 45Gy RT in 25 fractions. ARM B –Irinotecan 60mg once weekly for 4 weeks with oral Capacitabine 650 mg twice daily 5 days weekly with RT 45Gy in 25 fractions. The study is not yet approved.

EXPERT-C Trial addition of CETUXIMAB to Capacitabine /Oxaliplatin/RT. Primary end point-complete response. Improved overall survival rate is noted in KRAS wild type tumors

INDUCTION CHEMOTHERAPY-

GCR -3 trial before chemoradiation and resection a course of neoadjuvant chemotherapy –Cape OX regime ——induction therapy is tolerated and less toxic.

AVACROSS study (phase ii study)

Addition of Bevacizumab to induction chemotherapy the regime is well tolerated and complete pathological response 36%, this study is not approved and it is investigational currently**.**

MATERIAL AND METHODS

This study was conducted in the Department of Surgical Gastroenterology, Rajiv Gandhi Government General Hospital, Madras Medical college, Chennai.

Study period

From March 2012 to February 2014

Eligibility Criteria

- All patients with locally advanced operable rectal cancer i.e. T3, T 4, node positive tumors without distant metastasis
- Patients with histologically confirmed adenocarcinoma within 12 cm from anal verge(locally advanced growth in Middle and Lower third)
- Patients underwent sigmoid colostomy for intestinal obstruction
- Patients -Lower third Rectal growth with upper Anal canal involvement
- Radiological evidence of mesorectal invasion

Exclusion Criteria

- Patients who previously had cancer other than basal cell carcinoma of skin
- Patients who had received radiotherapy or chemotherapy
- Contraindications to chemoradiotherapy
- Tumor involving pelvic side walls, upper sacral vertebra, involving upper rectum
- Distant metastasis.
- Patients with poor performance status

Medical ethics committee of the hospital approved the study.

Preoperative evaluation

After obtaining informed written consent from patients, enrollment into the study done. Loco regional staging done with contrast enhanced CT of abdomen and pelvis, Endorectal ultrasound and cystoscopy in cases suspected of bladder invasion.

A lymph node metastasis of four or greater than four as detected by imaging was staged as N 2 disease. Distant metastasis was excluded by contrast enhanced CT of abdomen and pelvis, chest X-ray and if necessary a CT chest. Colonoscopy was done to rule out synchronous lesions.

A basic work up including complete hemogram, Renal function tests, Liver function tests, Tumor markers –CEA, Pulmonary function tests and Cardiac tests – ECG &Echocardiogram was done to rule out any major illness and to confirm the patient's fitness for surgery.

Treatment

Preoperative external beam radiotherapy was given for a total dose of 50.4 Gy in 28 fractions of 180 cGy each, five times per week for total duration of five and a half weeks. It was given as anterior and posterior opposed portals using Telecobalt machine of 1.33 meV. The radiotherapy was given to include the tumor area and its drainage lymph nodes (pelvic-internal, external iliac, obturator).

The upper margin of radiotherapy field was L 5-S 1. The lower margin was obturator foramen, 1.5 cm below lower border of pubic symphysis. The lateral margin was 1 cm lateral to true pelvis at level of mid inguinal point. If the tumor extended to anal canal, inguinal nodes were included in the field; laterally the radiotherapy field was extended to anterior superior iliac spine.

The chemotherapeutic agent used was 5 Flurouracil, used as a bolus of 350mg/m2 /d for 5 days, during the first and fifth weeks of radiotherapy along with 20mg/m2 of leucovorin. Postoperatively 5 Flurouracil was

given for four cycles (350mg/m /d, once in four weeks five times weekly) started postoperatively four weeks after surgery.

Surgery

Patients were assessed five weeks after surgery regarding the response to treatment - -either regression or progression of the disease by clinical as well as by radiological methods.

Decision for abdominoperineal excision of rectum, an anterior resection or pelvic exenteration was made preoperatively and modified according to the peroperative findings.

According to the standardized technique Total mesorectal excision was done. All patients who underwent anterior resection had a protective ileostomy. Patients with unresectable growth due to locally advanced disease had colostomy only.

During therapy, for signs of acute toxic effects requiring change in dosage or regimen patients were monitored weekly.

According to the Radiation Therapy Oncology Group criteria -Acute and long term toxic effects were graded with respect to acute and late adverse effects of radiotherapy. Patients were observed for Peroperative and postoperative complications which included bleeding, ileus, intestinal

fistulas, intra-abdominal abscess, perineal wound complications, urinary retention and death.

Follow up

Patients were followed at three monthly intervals for two years. Evaluations consisted of History and physical examination, a Complete blood count and Liver function tests and Renal function tests, Tumor marker -CEA, Proctoscopy, Abdominal ultrasonography, CT of Abdomen and Chest radiography (annual).

Local recurrence was to be confirmed histopathologically or by sequential radiological studies to detect mass lesion. Distal recurrence was confirmed histopathlogically.

All resected specimens were examined for histological grade, degree of fibrosis, resected margin status and nodal status. The primary end points analyzed were downsizing of tumor, down staging of the tumor, sphincter saving rates, toxicity of chemoradiotherapy, and patient compliance for the regimen. Secondary end points analyzed were the incidence of local recurrence, distal metastasis. Downsizing was defined as a reduction in the size of tumor after chemoradiotherapy as determined by physical examination. Down staging was defined as decrease in TNM stage, as assessed after chemoradiotherapy in the surgically resected specimen.

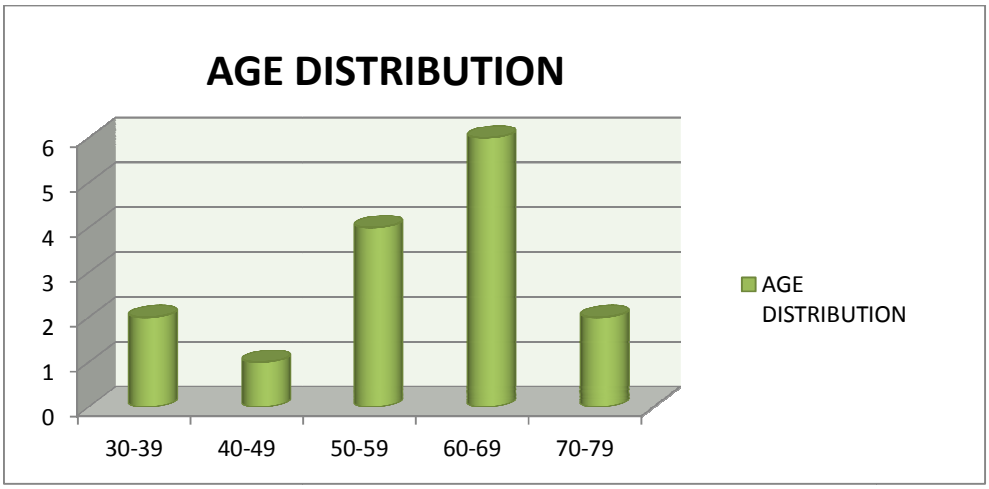
RESULTS

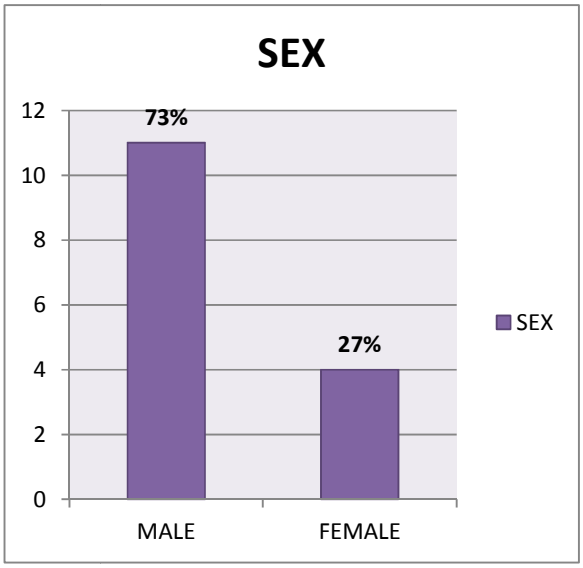
From March 2012 to February 2014, in the study fifteen patients were enrolled. chemotherapy given to all the patients as inpatient after prior complete hemogram examination. Radiotherapy given to the patient as inpatient or as outpatient admitted in the hospital whenever they developed complications, all the patients were periodically reviewed in our outpatient clinic and reported after completion of chemoradiotherapy. Fifteen patients underwent surgery after neoadjuvant chemoradiotherapy. Bleeding per Rectum is the predominant symptom. Their demographic characters are presented below.

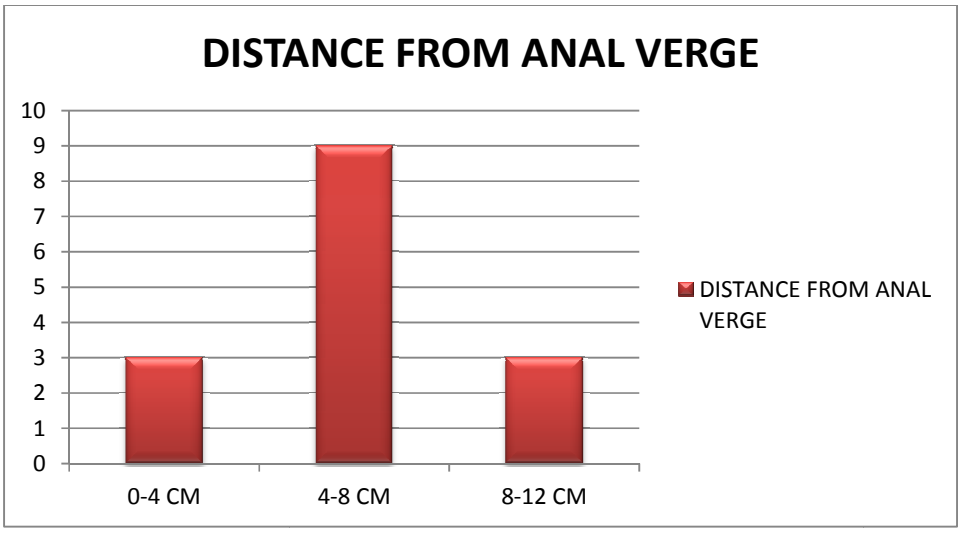
Age	Mean 58.4 yrs Range 37-73 yrs
Sex	Male 11(73%) Female 4 (27%)

Patients' age ranged from 37-73 years, mean age being 58.4 years. Eleven were males and four were females. Part of the tumors extended into anal canal from lower third of rectum into upper anal canal (20%). Nine patients had tumors involving lower rectum and Three had tumor involving middle third of Rectum.

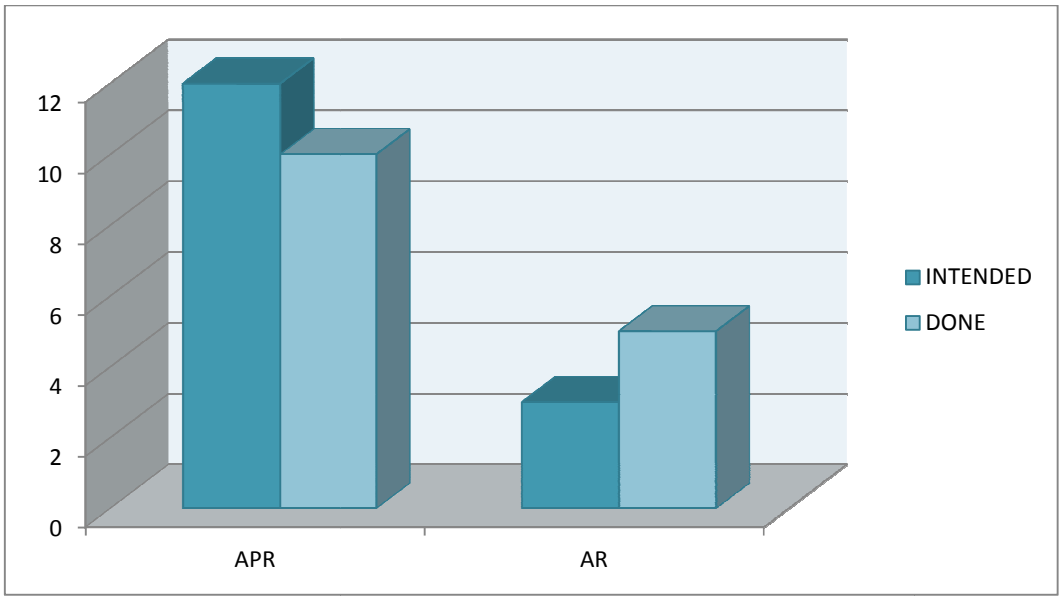
AGE	MEAN	58.4
	RANGE	37-73
SEX	MALE	11(73%)
	FEMALE	27(%)







Distance from anal verge	No (%)
0-4 cm	3(20%)
4-8 cm	9(60%)
8-12 cm	3(20%)



Histology Type	No (%)
Well differentiated	10 (66.66%)
Moderately differentiated	4(26.24%)
Poorly differentiated	1(6.66)

Tumor Characteristics

Clinical Stage of Tumor	**No (%)**
Stage I (T1,T 2, NO,MO)	0
Stage 2 A (T3, NO, MO)	3(20%)
Stage 2 B (T4, NO, MO)	1(6.66 %)
Stage 3 A (Tl, T2, Nl, MO)	0
Stage 3 B (T3, T4, Nl, MO)	9(60 %)
Stage 3 C (any T, N2, MO)	2 (13.32 %)
Stage 4 (any T, any N, M 1)	0

Surgical data

Interval to CRT and Surgery (in weeks)	**No of cases**
5	0
6	14
7	**1**
8	**0**

Surgery Performed	Number
Anterior resection	5(33.33%)
APER	10(66.66%)

Fourteen patients underwent surgery at six weeks after chemoradiotherapy; one patient had surgery after seven weeks in post chemoradiotherapy period. Five patients underwent anterior resection, none of the female patients had uterine or bladder involvement which was noticed in preoperative imaging as well as intra operative assessment. Ten patients underwent abdominoperineal resection. Patient with growth extension up to pelvic side wall which were inoperable were not included in the study and the patients were offered palliative sigmoid colostomy and they were not included in the study

Complications

Peroperative complications Bleeding	1
Post operative complications	
Abdominal wound infection	4
Perineal wound infection	3
Intra abdominal abscess	0
Urinary retention	2

Chemoradiotheray toxicity	3 (20 %)
Mild-Skin irritation & Discoloration	2(13.32%)
Vomiting	2(13.32%)
Diarrrhoea	1 (6.66 %)
Severe – Anaemia	1 (6.66 %)

One patient developed intraoperative bleeding due to injury to sacral plexus. It was controlled by packing. Minor complications occurred in four patients, developed abdominal wound infection which was treated conservatively by Antibiotics after confirming the sensitivity by culture.

One patient developed perineal wound gaping treated with thorough letting out the collection and thereafter with regular dressings. Two patients developed urinary retention in the postoperative period, was treated with continuous bladder drainage for one month. Fourteen patients in the series are treated by open approach; one patient underwent laparoscopic abdominoperineal excision of rectum.

One patient developed anemia requiring blood transfusion after the second dose of chemotherapy in the fifth week. Minor complications like skin irritation occurred in two patients, vomiting in two, diarrhea in one which was self-limiting.

Results of Surgery

Downsizing of Tumour	14/15 p
Downstaging of Tumour	12/15 p
Follow up Period	6 months-12 months (median- 9 months)
Local recurrence	Nil
Distant metastasis	Nil

Downsizing of tumor seen in fourteen of fifteen patients who had responded well to neoadjuvant chemoradiotherapy. In twelve of fifteen (12/15) patients down staging occurred

The follow up period ranged from six months to twelve months, with the median follow up period being nine months. No patient developed local recurrence. Distant metastases in the form of Liver metastasis not noted in any of the patients who had disease.

APER intended	Sphincter saving procedure
12	2/15(13.32)

Of the twelve patients who had been treated for locally advanced carcinoma Rectum for whom APER was planned, a sphincter conservation surgery was possible in two of them after neoadjuvant chemoradiotherapy

and those patients underwent anterior resection. Before neoadjuvant chemoradiotherapy only three anterior resections were planned. After it, five anterior resections were done with covering ileostomy done to protect the anastomosis as well as to reduce leak related complications.

Postoperative TNM staging

(T1.T2.N0, MO) Stage 1	3 (20 %)
(T3,N0, MO) Stage 2 A	6 (20%)
(T4, NO, MO) Stage 2 B	0
(Tl, T2, Nl, MO) Stage 3 A	2(13.2%)
(T3, T4, Nl, MO) Stage 3 B	4 (26.64 %)
(any T, N2, MO) Stage 3 C	0
(any T, any N, Ml) Stage 4	0

Anterior resections intended	Anterior resections done
3(20%)	5 (33.3%)

Neoadjuvant chemoradiotherapy increased sphincter conservation in 2/15 patients in our study.

Patient compliance

Fifteen of the fifteen patients had completed the full course of chemoradiotherapy followed by surgery (100%) with minimal toxicities to chemoradiotherapy treatment.

DISCUSSION

Over the last few years Significant advances are made in the colorectal cancer. Management is altered by more thorough understanding of the molecular basis for this disease, coupled with the development of new therapeutic approaches and expertise in management. Approach in the workup and disease staging of the patients is altered by new strategies for screening and for the detection of recurrent disease by careful postoperative follow up.

Preoperative Chemoradiotherapy

The rationale for giving preoperative chemoradiotherapy is to improve the survival and the advantage of delivering both the agents preoperatively. These advantages include improved compliance given before a major surgery in well vascularized setting to assist in down staging to enhance the rate of curative surgery, prevents tumor tract seeding at surgery by sterilizing the tumor field and permit sphincter preservation in low lying rectal tumors. Irradiation is more effective is better if given preoperatively due to better tumor oxygenation.

The sphincter conservation rate also doubled after preoperative chemo radiotherapy. Postponing the surgery to six weeks help in shrinkage

of tumor and recovery of tissues after treatment before fibrosis sets in. Higher pathological complete response produced by addition of 5FU to preoperative radiotherapy over radiotherapy alone[13]

No improvement in disease-free survival (DFS) or overall survival but Better locoregional control

About 30% patients develop distant metastases.

Due to Better pCR and loco regional control rates, 5- FU-based preoperative chemo radiotherapy followed by total mesorectal excision has become the standard of care in patients with locally advanced rectal cancer.

Current chemoradiotherapy schedules have been empirically developed. More recently, oxaliplatin and irinotecan have been explored to increase tumor shrinkage prior to surgery within chemo radiotherapy schedule, There is no widely accepted optimal timing, schedule, sequence either in terms of the drugs or RTdose.

High levels of normal tissue damage, including small bowel injury, nerve dysfunction rectal bleeding, impaired Sphincter function, vaginal stenosis, , and sacral fractures with Radical pelvic RT at doses of 55-60 Gy.

40-50 Gy in 1.8- to 2.0-Gy fractions Lower radiotherapy doses have become established as a standard, because it is associated with a good tumor response and with more acceptable levels of late morbidity.

Downsizing of tumour

Study	Downsizing	p value
Polish Trial [13] 2004	Present	p <0.001
German Rectal Cancer Study group[12] 2004	Present	p < 0.001 .
EORTC trial 22921[17] 2005	Present	p <0.001
This study	Present	

Neoadjuvant chemo radiotherapy helps significant downsizing of tumor as it causes tumor shrinkage. In this study downsizing occurred. This is almost in accordance with other studies which have shown similar significant regression of the tumor after chemoradiotherapy.

Downsizing is indicator of good response to preoperative chemoradiotherapy. This is concurrence with the results of Polish trial the tumor was 1.9 cm smaller in patients after chemoradiotherapy

Study	Down Staging	Percentage of patients downstaged
Rich et **al**[2U], 1995	Present	64 %p<0.01
German Rectal Cancer Group Trial [12] 2004	Present	62 %p <0.001
EORTC Trial 22921 [17] 2005	Present	52 % p < 0.001
Chung Wah Lam et al [4] 2005	Present	69 %p<0.01%
This study	Present	

After preoperative chemoradiotherapy, postoperative histopathology shows downgrading of the tumor. In this study of showed down staging (p <0.0001). A good pathological response is a good prognostic indicator, with patients having a good response having fewer incidences of improved overall survival and local recurrence l. Chung Wah Lam et al [4] in 2005 has shown that 69 % of his patients had decreased tumor stages after chemoradiotherapy.

Preoperative TNM Staging Vs Post-operative TNM Staging This Study

Stage	Preoperative TNM	Postoperative TNM
Stage 1 (Tl,2, NO, MO)	0	3
Stage 2 A (T3, NO, MO)	3	6
Stage 2 B (T4, NO, MO)	1	0
Stage 3A (T1,T2, Nl, MO)	0	2
Stage 3B (T3, T4, Nl,MO)	9	4
Stage 3 C (any T, N2, MO)	2	0
Stage 4 (any T, any N, Ml)	0	0

In this study preoperatively around 60% of the tumors were in stage 3 B. Post-operative, histopathology showed a significant shift towards lower stages stage.

2A in 20% and 20 % in stage 1. Due to the tumoricidal effect of chemoradiotherapy the lymph node positivity was reduced.

Effect of time interval on surgery and down staging

Long time interval between radiotherapy and surgery led to sphincter preservation because of tumor down staging When the optimum time interval between radiotherapy and surgery was analyzed.

In 1999 Francois et al, conducted a randomized trial to compare short interval outcome with long interval of 6-8 weeks. A long interval between preoperative radiotherapy and surgery was associated with pathologic down staging (10.3% in the SI group v 26% in the LI group, P .005) and a significantly better clinical tumor response (53.1% in the SI group Vs 71.7% in the LI group, P.007) . No differences in morbidity, local relapse, and short-term survival noted between the two groups at a median follow-up of 33 months.

Sphincter-preserving surgery was performed in 76% of cases in the LI group versus 68% in the SI group ($p < 0.27$).He concluded that a long interval between preoperative irradiation and surgery provides increased tumor down staging. In questionable sphincter preservation, a long interval may increase the chance of a successful sphincter- saving surgery.

The ideal time interval is 6 weeks [56, 21,28] for surgery after radiotherapy when there is an optimal tumor response and further delay does not enhance the effect of radiotherapy. When fibrosis sets in, dissection also becomes technically difficult with increased incidence of complications like intra-abdominal sepsis, increased bleeding. In this study, the interval ranged from 6 to seven weeks, median being six weeks.

Sphincter Saving Procedures after neoadjuvant chemoradiotherapy

Study	Sphincter saving	Percentage
Rich et al[20] 1995	Present	66.6 %
NSABP Trial [14] 1997	Present	50 %
Polish Trial [13] 2004	Present	58 %
German Rectal Cancer Group Trial [12] 2004	Present	39 %
Chung Wah Lam et al [4] 2005	Present	82 %
This study	Present	13.12 %

One of the advantages of preoperative chemoradiotherapy is that tumor downsizing helps sphincter saving procedures. The incidence of sphincter saving procedures range from 39 % up to 82 %. In this study, preoperatively only three patients were planned for an anterior resection.

After neoadjuvant therapy, anterior resection was possible in five patients, sphincter conservation rates were increased. The lower number of sphincter saving procedures is due to the fact that most of the tumors (66.6 %) had already extended into the anal canal, necessitating abdominoperineal excision of rectum.

Distal Resection Margin after Neoadjuvant chemoradiotherapy

Nearly 50% of patients undergo Abdominoperineal excision of rectum despite the increasing use of sphincter preservation for rectal cancers. In many circumstances, for adequate distal margins, Abdominoperineal excision of rectum is performed.

More limited distal margins may be appropriate as per evidence. For low lying rectal tumors doing an abdominoperineal excision does not increase the radicality of the procedure or improve survival. Study by Paty et al found that no increase in pelvic recurrence when the distal margin was <2 cm compared with >2cm. 1 cm distal margins are adequate as per recent evidence'[22]. in the past, distal margins as great as 5 cm were advocated

Smaller distal margins, even 1 cm, may be adequate, supported by pathological evidence that distal intramural spread rarely exceeds 1 cm .A number of clinical pathological studies [2 2] that examined distal intramural

spread suggest that. When significant distal spread does occur, long term survival is affected adversely, despite abdominoperineal excision of rectum. The presence of distal spread is associated with decreased survival due to recurrence (mainly in lung). The use of centimeter and sub centimeter margins is controversial.

Jose G Guillem et al [25] on prospective pathological analysis of whole mount sections of rectal cancer following combined modality therapy in 109 patients has shown that intramural extension occurred only in 1.8 % patients (<0.95 cm). Hence he concluded 1 cm margins are sufficient after preoperative chemoradiotherapy and this increases the chances of sphincter preservation without increasing the chances of local recurrence.

Preoperative chemoradiotherapy also reduces circumferential resection margin positivity. Circumferential resection margin positivity is as high as 25 % if no preoperative chemoradiotherapy is used. In this study a distal margin of one cm did not result in margin positivity in any of the postoperatively examined specimens.

Local Recurrence

Study	Duration of follow up	Local Recurrence	Percentage
EORTC Trial ^984	7 years	Present	15 %
Rich et al [20] 1995	2 years,3 months	Present	*4%*
Polish Trial [13] 2004	4 years	Present	14.2 %
German Rectal Cancer Group Trial [12] 2004	4 years	Present	*6%*
EORTC Trial 22921 [17] 2005	5.4 years	Present	8 %
Jean Pierre Gerard et al [19] FFCD 9203, 2006	81 months	Present	8.1 %
This study	9 months	Nil	0%

Local recurrence

Tumor factors

- Tumor invasion beyond muscle(T3 to T4)
- Nodal involvement
- poor differentiation,
- Mucin production and venous or lymphatic invasion.
- CRM positivity
- Intestinal obstruction,

- Tumor Perforation

Tumor adherence to other local organs

Molecular Features

- Aneuploidy
- Mutation in p53
- Loss of heterozygosity at chromosome 18q.
- microsatellite instability- poor

Technical Factors

Tumors in the distal rectum

Locally extensive tumors are far more likely to recur than mobile tumors, which type of procedure is performed does not matter. Local recurrence is significantly higher in patients who have circumferential involvement than those without involvement. Recurrence is also influenced by site of lesion in rectum, lower one third tumors have higher incidence than upper third tumors. Incomplete removal of tumor is a very important cause for local recurrence

Local recurrence ranges from 5.8% as reported by Kapitjein et al[24] to 15 %. TME considered as a contributing factor in reducing pelvic recurrences to as low as 5% to 8% in high-risk patients

Follow up of this study during a ranging from 6 months to 9 months and no evidence of local recurrence is noted. This correlates well with the response to chemoradiotherapy and an adequate TME as evidenced by downsizing and down staging.

Quirke et al. demonstrated that radial spread into the mesorectum is a common occurrence. Sharp dissection along the parietal pelvic fascia ensures resection of (5 mm) occult nodal metastases which may be left behind and causing local recurrence.

Radial margins are a more important predictor of disease recurrence and survival than distal margins.

There is an increased risk of recurrence for patients who undergo have abdominoperineal excision of rectum and reflects the worse prognosis attributed to tumors of the low rectum. The location of the tumor may be a more important prognostic factor.

Toxicity of chemoradiotherapy

Study	Mild Toxicity (%)	Severe Toxicity(%)
German Rectal Cancer Group Trial [12] 2004	*12*	27
EORTC Trial 22921 [17] 2005	38.4	13.9
This study	26.66	6.66

About 26.6 % of patients developed toxicity of chemoradiotherapy. Skin irritation and discoloration was the most common toxicity encountered. It was totally reversed after few weeks. This is comparable with other studies showing a range of 11 % to 15 %. The EORTC 22921 trial showed a very high toxicity of 38.4 %. In this study no patient had a change in the chemoradiotherapy schedule due to toxicity.

Postoperative complications

Study	**Complications(%)**
German Rectal Cancer Group Trial [12] 2004	36
EORTC Trial 22921 [17] 2005	22.8
Jean Pierre Gerard et al [19] FFCD 9203, 2006	20.9
This study	26.7

There is always a fear that neoadjuvant chemoradiotherapy increases preoperative complications, delays wound healing, and patients may need perineal flap cover to prevent post-operative wound disruption. The postoperative complications in this study were 26.7 % only. Of ten patients who underwent only on abdominoperineal excision of rectum only one developed perineal wound complication which was successfully treated conservatively. So preoperative chemoradiotherapy can be given safely with good patient compliance, minimal side effects and less postoperative complications..

Effect on survival

With preoperative radiotherapy alone Randomized controlled studies have not shown any significant survival benefit.

Jose G.Guilem et al[23] " analyzed the long term outcome following preoperative combined modality therapy and total mesorectal excision of locally advanced rectal cancer, estimated 10-year overall survival was 58% and 10 year recurrence-free survival (RFS) was 62%. With a median follow-up of 44 months

Lymph vascular invasion and/or perineural invasion (PNI), pathologic response of greater than 95%, and positive lymph nodes were significantly associated with disease free survival and overall survival.

CONCLUSION

Neoadjuvant chemoradiotherapy given in stage 2/ middle and low rectal cancers causes significant downsizing, down staging of the tumor, increases the rate of sphincter conservation surgeries.

The toxicity of chemoradiotherapy is minimal, patient compliance is good.

The postoperative complications are not increased and it helps decrease the incidence of local recurrence.

The effect on survival has to be determined on long term follow up only. Hence it is beneficial to administer it to patients with stage 2/3 middle and low rectal cancers.

REFERENCES

1. S. Boulis Wassif, Gerard MD, J Loygue. Final Results of a Randomized Trial on the Treatment of Rectal Cancer With Preoperative Radiotherapy Alone or in Combination With 5-Fluorouracil, Followed by Radical Surgery, Trial of the European Organization on Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group, Cancer 1984; 53: 1811-1818

2. Heald RJ, Moran BJ, Ryall RD et al. Rectal cancer: The Basingstoke experience of total mesorectal excision, 1978-1997. Arch Surg.1998; 133; 894-899.

3. N.Arbman G, NilssonE , Local recurrence following TME for rectal cancer; BJS 83: 375-79.

4. Chung-Wah Lam, William Tzu-Liang Chen, Effect of preoperative concurrent chemoradiotherapy in locally advanced low rectal cancer after radical resection surgery . Int Surg 2005: 90: 53-59

5. Jin C Kim, Keiichi Takahashi et al, Comparative outcome Between Chemoradiotherapy and Lateral Pelvic Lymph Node Dissection Following Total Mesorectal Excision in Rectal Cancer, Ann Surg 2007; 246; 754-762

6. Masato Kusunoki et al, Current Surgical management of Rectal Cancer, Dig Surg 2007:24:115-119

7. Steams MW Jr, Learning RJ et al . Irradiation in inoperable rectal cancer . JAMA 1975; 231:1388

8. Swedish Rectal Cancer Trial Group. Improved survival with preoperative radiotherapy in respectable rectal cancer. N Engl J Med 1997; 336; 980-987.

9. Frykholm GJ, Pahlman L, Glimelius B. Combined chemo and radiotherapy vs. radiotherapy alone in the treatment of primary, nonresectable adenocarcinoma of the rectum. Int J Radiat Oncol Biol Phys 2001;50:433-440.

10. Ruo L, Tikoo S, Klimstra D. Long term prognostic significance of extended rectal cancer response to preoperative radiation and chemotherapy. Am J Surg 2002; 236: 75-81.

11. Roh M, Petrelli N, Wieand H. Phase III randomised trial of preoperative versus postoperative multimodality therapy in patients'with carcinoma of the rectum (NSABP R-03). J Clin Oncol 2001; 20(suppl 1): 123a

12. Sauer R, Becker H. Hohenberger W et al. German Rectal Cancer Study Group. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731-1740.

13. Bujko.K, Nowacki MP, Nasierowska-Guttmejer A et al. Sphincter preservation following preoperative radiotherapy for rectal cancer:

Report of a randomised trial comparing short-term radiotherapy vs. conventionally fractionated radiochemotherapy. Radiother Oncol 2004; 72: 15-24.

14. Hyams DM, Mamounas EP, Petrelli N et al. A clinical trial to evaluate the worth of preoperative multimodality therapy in patients with operable carcinoma of the rectum: A progress report of National Surgical Breast and Bowel Project Protocol R-03. Dis Colon Rectum 1997; 40:131-139.

15. RobGlynne-Jones, Mark Harrison. Locally Advanced Rectal Cancer: What Is the Evidence for Induction, Oncologist 2007; 12; 1309-1318

16. Gerard JP, Chapet O, Nemoz C et al. Improved sphincter preservation in low rectal cancer with high-dose preoperative radiotherapy: The Lyon R96-02 randomized trial. J Clin Oncol 2004; 22: 2404-2409.

17. Jean-Frangois Bosset, M.D., Laurence Collette, Ph.D., Gilles Calais, M.D., Laurent Mineur, M.D., and Jean-Claude Oilier, M.D., for EORTC Radiotherapy Group Trial 22921 Chemotherapy with Preoperative Radiotherapy in Rectal Cancer N Engl J Med 2006; 355: 1114-23

18. Bosset JF, Calais G, Mineur L et al. Enhanced tumoricidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: Preliminary results- EORTC 22921. J Clin Oncol 2005; 23: 5620-5627.

19. Jean-Pierre Gerard, Thierry Conroy, Franck Bonnetain,Seitz, Bruno Buecher, Remy Mackiewicz, Michel Ducreux, and Laurent Bedenne. Preoperative Radiotherapy With or Without Concurrent Fluorouracil and Leucovorin in T3-4 Rectal Cancers: Results of FFCD 9203 . J Clin Oncol 24: 4620-4625.

20. Rich TA, Skibber JM, Ajani JA, et al. Preoperative infusional chemoradiation therapy for stage T3 rectal cancer. Int J Radiat Oncol Biol Phys 1995; 32: 1025-9.

21. Yves Francois et al, Influence of the time interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter sparing surgery: The Lyon R 90-01 randomized trial; J of Clinical Oncology, Voll7, No8, 1999, 2396-2402.

22. Boris Kuvshinoff, Irfan Maghfoor, Brent Miedema, David Ota

23. Distal Margins requirements after preoperative Chemoradiotherapy for distal rectal carcinomas: Are <=1 cm margin sufficient ?: Annals of Surgical Oncology: 8(2): 163-169.

24. Jose G .Guillem,David B Chessin, Jinru Shia, A Prospective Pathologic Analysis Using Whole Mount Sections of Rectal Cancer Following Preoperative Combined Modality Therapy, Implications For Shincter Preservation; Ann Surg 2007; 245; 88- 93.

25. Kapitjein E, Marijnen CA, Nagtegaal ID et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001;345;638-646

26. Jose G. Guillem et al. Long-term Oncologic Outcome Following Preoperative Combined Modality Therapy and Total Mesorectal Excision of Locally Advanced Rectal Cancer, Ann Surg 2005; 241: 0829-838)

27. Karanjia ND, Schache DJ, North WRS, Heald RJ. "Close shave" in anterior resection. Br J Surg 1990; 77: 510-2.

28. Moore HG, Riedel E, Minsky BD et al. Adequacy of 1 cm distal margin after restorative rectal cancer excision with sharp mesorectal excision and preoperative combined modality therapy. Ann Surg oncology.2003: 10: 80-85.

29. Cam-Ly Tran, Sejal Udani, Aliucia Holt, Tracey Amell. Evaluation of safety of increased time interval between chemoradiation and resection for rectal cancer; American Journal of Surgery; 2006; 192; 873-877.

30. Claudus Rodel, Peter Martus, Prognostic significance of Tumour Regression after Chemoradiotherapy for rectal cancer: J of Clinical Oncology, 2005; 23, 8688- 8696.

31. Bujko K, Nowacki MP ,Long term results of a randomized trial

comparing preoperative short course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. BJS 2006, Oct: 93(10): 1215-23.

32. Morita T, Murata A, Koyama M: CuiTent status of autonomic nerve preserving surgery for mid and low rectal cancers: Japanese experience with lateral node dissection. Dis of Colon Rectum 2003; 46; S 78-S87.

33. Medical Research Council Rectal Cancer Working Party. Randomised trial of surgery alone versus radiotherapy followed by surgery for potentially operable locally advanced rectal cancer. Lancet 1996; 348; 1605-1610

34. Rullier E,Goffre B, Bonell C. Preoperative radio-chemotherapy and sphincter saving resection in T3 carcinomas of lower third of rectum. Am surg 2001; 234; 633-640.

35. Ruo L, Tikoo s, klimstra D. Long term prognostic significance of extended rectal cancer response to preoperative radiation and chemotherapy. Am J Surg 2002; 236; 75-81.

36. Bujko J, kepka L, Michalski et al. Does rectal cancer shrinkage induced by by preoperative chemoradiotherapy increase the likelihood of anterior resection ? A systematic review of randomized trials. Radiotherapy Oncology 2006; 80; 4-12.

37. Roh Ms,colangelo L,Wieand S et al.Response to preoperative multimodality therapy predicts survival in patients wirh carcinoma of rectum.J Clinical oncology 2004;22;246s

38. Enker WE, Thaler Ht, Cranor Ml et al. Total Mesorectal excision in the operative treatment of carcinoma rectum. J Am Coll Surg. 1995; 181; 335-346.

39. de Haas-Kock DF, Baeten, Jager JJ et al. Prognostic significance of radial margins of clearance in rectal cancer. Br J Surg.1996; 83; 781-785.

40. WibeA, Syse A, Andersen E et al. Oncological outcomes after total mesorectal excision for cure for cancer of lower rectum:anterior vs abdominoperineal excision. Dis Colon rectum 2004; 47; 48-58

41. Williams NS, Durdley P, Johnston D: The outcome following Sphincter saving resection and abdominoperineal resection of rectum for low rectal cancer; Br J Surg 1985; 72;595-598.

42. Law WL, Chu KW. Abdominoperineal excision is assosciatecl with poor Oncological outcome. Br J Surg 2004; 91; 1493-1499.

43. Tveit KM. Guldvog 1, Hagen S, et al. Randomized controlled trial of postoperative radiotherapy and short term time scheduled 5 -FU against surgeryalone in treatment of Dukes B and C rectal cancer, Norwegian Adjuvant Rectal Cancer Group. Br J Surg 1997; 84; 1130-1135.

44. Bouzourene H, Bosnian FT, et al. Importance of tumour regression assessment in predicting outcome in patients with locally advanced rectal carcinoma who are treated with preoperative radiotherapy. Cancer 2002 ; 94; 1121-1130.

45. Moore HG, Gittleman AE, Minsky BD, et al: Rate of pathological response with increased time interval between preoperative combined modality therapy and rectal cancer excision. Dis Colon Rectum 2004; 47; 279-286, 46.

46. Heimann TM , Szporn A, Bolnick K et al. Local recurrence following surgical treatment of rectal cancer. Dis Colon Rectum; 1986; 29; 862-864.

47. Holm T, Rutqvist LE, Johansspon H et al. Postoperative mortality in rectal cancer treated with and without radiotherapy;causes and risk factors, Br J Surg 1996; 83; 964-968; 48

48. Bokey EL, Chapuis PH , Dent OF. Factors affecting survival after excision of the rectum for cancer. Dis Colon Rectum 1997; 40; 3-10.

49. Grann A, Minsky BD, Cohen AM, et al. Preliminary results of preoperative 5 fluorouracil, low dose leucovorin and concurrent radiation therapy for respectable T rectal cancer. Dis Colon Rectum 1997; 40; 515-522.

50. Wichmann MW, Muuller C, Meyer G, Strauss T, Homung HM et al. Effect of preoperative chemoradiotherapy on lymphnode retrieval after resection of rectal cancer. Arch Surg 2002; 137; 206-210.

51. Lavery IC, Lopez-Kostner F, Fazio VW, Fernandez Martin M et al. Chances of cure are not compromised with sphincter saving procedures for cancer of the lower third of rectum.Surgery . 2002; 122; 779-785.

52. Emami B, Pilepich M, Willett C et al. Effect of preoperative irradiation on resectability of colorectal carcinomas. Int J Radiat Oncol Biol Phys. 1982; 8: 1295— 1299

53. Aschele, Carlo, et al., PrimaryTumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. J Clin Onc. Published online before print. Doi: 10.1200/JCO.2010.34.4911

54. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial-The Lancet Oncology, Volume 13, Issue 7, Pages 679 - 687, July 2012

55. 2010 by American Society of Clinical Oncology-Comparison of Two Neoadjuvant Chemoradiotherapy Regimens for Locally

Advanced Rectal Cancer: Results of the Phase III Trial ACCORD 12/0405-Prodige 2

56. ARISTOTLE Trial- ARISTOTLE: a phase III trial comparing standard versus novel chemoradiation treatment (CRT) as pre-operative treatment for magnetic resonance imaging (MRI)-defined locally advanced rectal cancer

57. Dis Colon Rectum. 2013 Jul;56(7):921-30. Timing of surgery after long-course neoadjuvant chemoradiotherapy for rectal cancer: a systematic review of the literature.Foster JD[1], Jones EL, Falk S, Cooper EJ, Francis NK.

CASE REPORT FORM

Name- Age- Sex-

Address-

Occupation (level)-

H/o abdominal pain

H/o Bleeding PR/ Mucus discharge H/O Constipation

H/o straining for stools and sense of incomplete evacuation

H/o loss of appetite H/o loss of weight

H/o abdominal distension H/o vomiting

H/o fever H/o comorbid illness

DM, SHT,BA,TB,IHD

General examination

Respiratory system examination

Cardiovascular system examination

Abdominal examination

Per Rectal examination

Left supraclavicular node examination

Investigations

Complete blood count	Serum electrolytes
Blood sugar	Renal function tests
Urea	Serum creatinine
Liver function tests	Bilirubin
SGOT	SGPT
SAP	Serum albumin
Prothrombin time	
ECG	
Chest X-ray	
X-ray abdomen	
Echocardiogram	

Ultrasonogram abdomen

Barium enema

Upper GI endoscopy

Lower GI endoscopy

CECT Abdomen and Pelvis

Ostomy counseling

Family counseling

Informed consent including high risk procedure, postoperative ICU care for monitoring and ventilator support and resurgery in case of complications

Type of surgical Procedure

Outcome

Wound infection

Respiratory infection

Anastomotic leak

In hospital stay

In hospital mortality

INFORMED CONSENT FORM

Title of the study -**"Analysis of Presentation, Management and outcome following Neoadjuvant therapy in Carcinoma Rectum"**

Name of the participant:

of age and, exercising

my free power of choice, hereby give my consent to be included as a participant in ___

_____

Name of the Principal/Co-Investigator: _____

Name of the Institution: Department of surgical gastroenterology, Madras Medical College and Rajiv Gandhi government general hospital, Chennai. .I,_____(name of participant), have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years.

(1) I have read and understood this consent form and the information provided to me.

(2) I have had the consent document explained to me.

(3) I have been explained about the nature of the study.

(4) I have been explained about my rights and responsibilities by the investigator.

(5) I have informed the investigator of all the treatments I am taking or have taken in the past _____ months including any native (alternative) treatments.

(6) I have been advised about the risks associated with my participation in the study.

(7) I agree to cooperate with the investigator and I will inform him/her immediately if I suffer unusual symptoms.

(8) I have not participated in any research study within the past _____ month(s).

(9) [I have not donated blood within the past _____months

(10) I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in the hospital

(11) I am also aware that the investigators may terminate my participation in the study at any time, for any reason, without my consent.

(12) I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Government agencies, and ethics committee. I understand that they may inspect my original records.

(13) I understand that my identity will be kept confidential.

(14) I have had my questions answered to my satisfaction.

(15) I consent voluntarily to participate as a participant in the research study.

I am aware, that if I have any questions during this study, I should contact the investigators. By signing this consent from, I attest that the information given in this document has been clearly explained to me and understood by me. I will be given a copy of this consent document.

For adult participants

Name and signature / thumb impression of the participant (or legal representative if participant
incompetent):

(Name) _____(Signature)_____ Date: _____

Name and signature of impartial witness (required for illiterate patients):

(Name) _____ (Signature)_____

Date:_____

Address and contact number of the impartial witness:

_____

Name and signature of the Investigator or his representative obtaining consent:

(Name) _____ (Signature)_____

(Date)_____

Name and signature / thumb impression of the participant's parent(s) (or legal representative

INFORMATION TO PARTICIPANTS

Title: - **"Analysis of Presentation, Management and outcome following Neoadjuvant therapy in Carcinoma Rectum"**

Principal Investigator:

Co-Investigator (if any):

Name of Participant:

Site:

You are invited to take part in this research/ study/procedures/tests. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns.

What is the purpose of research? Improved overall survival and decreased local recurrence rates have been achieved For locally advanced rectal cancers ,with neoadjuvant chemoradiation therapy (CRT) which leads to a decrease in tumor size and enhances the possibilities of tumor resectability and sphincter preservation These symptoms may last for _____(usual course of the disease*)*. We want to test the efficacy and safety of a new _____ (drug / intervention / surgery /procedure/lab test) in this disease/condition. We have obtained permission from the Institutional Ethics Committee.

The study design- Retrospective study

Study Procedures The study involves evaluation of Carcinoma Rectum treated with neoadjuvant therapy for which we will need tumor markers, barium enema colonoscopy, CECT abdomen & pelvis. The planned scheduled involve visits at _____,_____,____,and_____(days/ weeks) after your initial visit. You will be required to visit the hospital _____ number of times during the study.

At each visit, the study physician will examine you. Some [blood / urine /imaging/clinical examination other] tests will be carried out at each visit. [… … ml of blood will be collected at each visit. Blood collection involves prick with a needle and syringe.] These tests are essential to monitor your condition, and to assess the safety and efficacy of the treatment given to you.In addition, if you notice any physical or mental change(s), you must contact the persons listed at the end of the document. You may have to come to the hospital (study site) for examination and investigations apart from your scheduled visits, if required.

Possible risks to you – If any, Briefly mention

Possible benefits to you - If any, briefly mention

Possible benefits to other people

The results of the research may provide benefits to the society in terms of advancement of medical knowledge and/or therapeutic benefit to future patients.

Confidentiality of the information obtained from you

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history). By signing this document, you will be allowing the research team investigators, other study personnel, sponsors, Institutional Ethics Committee and any person or agency required by law like the Drug Controller General of India to view your data, if required.

The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

How will your decision to not participate in the study affect you?

Your decision not to participate in this research study will not affect your medical care or your relationship with the investigator or the institution. You will be taken care of and you will not loose any benefits to which you are entitled.

Can you decide to stop participating in the study once you start?

The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during the course of the study without giving any reasons. However, it is advisable that you talk to the research team prior to stopping the treatment/discontinuing of procedures etc.

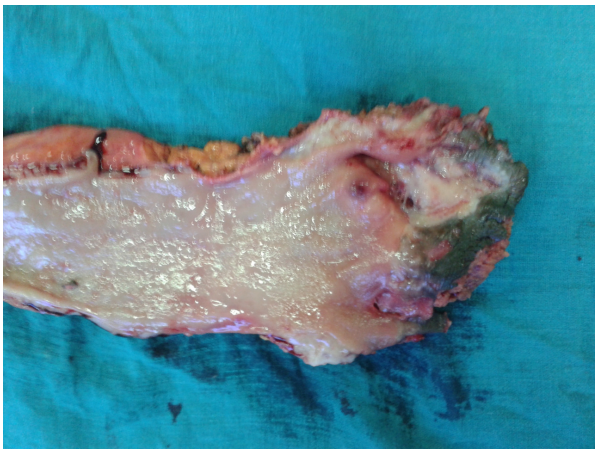
Signature of Investigator	Signature of Participant
Date	Date

MASTER CHART

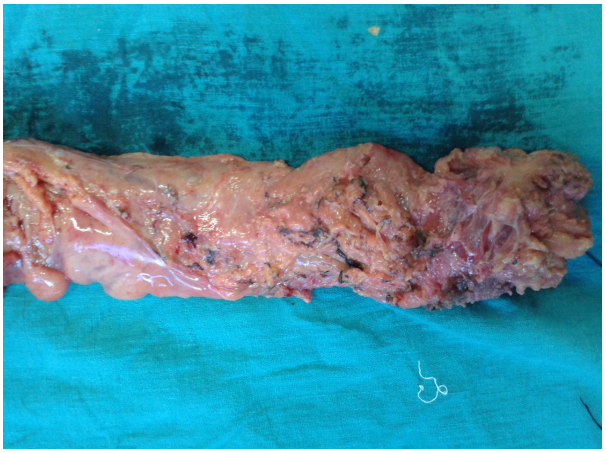
No	Name	Age & sex	Presentation	Location of tumor	Staging of tumor	Comorbid	Total dose of Radiotherapy (Gy)	Number of fractions	Chemotherapy Drugs	surgery	Duration of treatment
1	LOGANATHAN	70/M	Bleeding PR	Lower Rectum	T3 N2 M0	HT	50.4	28	5 FU Cisplatin	APER	4 MONTHS
2	MANOHARAN	58/M	Bleeding PR	Middle & Lower Rectum	T3NX M0	HT	50.4	28	Cisplatin	Low Anterior resection	3.5 months
3	BALASUBRAMANIAN	63/M	Altered bowel habits	Lower rectum	T4a N0M0	-	50.4	28	5fu cisplatin	APER	4 Months
4	PARTHASARATHI	53/M	Bleeding PR	Lower Rectum	T4A N1 M0	-	50.4	28	OXALIPLATIN CAPACITABINE	APER	3.5 Months
5.	VELLAIKANNU	73/M	Bleeding PR	Lower Rectum	T3N2M0	-	50.4	28	OXALIPLATIN CAPACITABINE	Low Anterior Resection	6 months
6	MANGAMMAL	65/F	Bleeding PR	Middle rectum	T3N1M0	-	50.4	28	CISPLATIN 5FU	Anterior resection	6 months
7	SIVA SANKARI	38/F	Bleeding PR	Middle third rectum	T3N1M0	-	50.4	28	CISPLATIN 5FU	Anterior Resection	6 months
8	VAITHYALINGAM	68/M	Bleeding PR	Lower Rectum	T3N1M0	HT	50.4	28	CISPLATIN 5FU	APER	4 months
9	RAVI	48/M	Constipation	Lower Rectum	T4a N1 M0	-	50.4	28	CISPLATIN 5FU	APER	4 Months
10	RUKMANI	65/F	Bleeding PR	Lower Rectum	T3N1M0	-	50.4	28	OXALIPLATIN CAPACITABINE	APER	4 Months
11	SESHAKUMAR	37/M	Incomplete evacuation	Lower Rectum	T3N1M0	-	50.4	28	OXALIPLATIN CAPACITABINE	APER	4 Months
12	DURAISAMY	55/M	Difficulty in passing motion	Lower Rectum	T3 N0 M0	HT	50.4	28	CAPACITABINE OXALIPLATIN	APER	4 Months
13	LALITHA	60/F	Bleeding PR	Lower Rectum	T3N1 MX	HT	50.4	28	CISPLATIN 5FU	APER	4 Months
14	ARUMUGAM	66/M	Bleeding PR	Lower Rectum	T3NXM0	HT	50.4	28	CISPLATIN 5FU	APER	4 Months
15	MANI	57/M	Bleeding PR	Middle and Lower Rectum	T3N1M0	-	50.4	28	CISPLATIN 5FU	Anterior resection	4 Months

Number	SURGERY	DURATION (minutes)	BLEEDING (ml)	ILEOSTOMY	WOUND INFECTION	LEAK RATE	SPHINCTER PRESERVATION	HISTOLOGY (diifferentiation)	Referral pattern	Previous surgery	diet
1	APR	150	400	-	-			Well	Self	nil	Mixed
2	AR	170	500	+	+	_	+	Well	Self	Nil	Mixed
3	APR	200	600	-	-			Well	Self	Nil	Mixed
4	APR	120	300		-			moderate	Self	Nil	Mixed
5	AR	170	300	+	-		+	Well	Doctor	Haemorrhoidectomy	Mixed
6	AR	140	250	+	+	+	+	Well	Self	Nil	Mixed
7	AR	140	280	+	-		+	Moderate	Self	Nil	Mixed
8	APR	120	320		-			Well	Doctor	Haemorrhoidectomy	Mixed
9	APR	120	330		-			moderate	Self	Nil	Mixed
10	APR	110	200		-			Well	Self	nil	Mixed
11	APR	130	250		-			Poor	Doctor	Haemorrhoidectomy	Mixed
12	APR	120	270		-			Well	Self	nil	Mixed
13	APR	110	250					moderate	Self	nil	Mixed
14	APR	130	200		+			Well	Doctor	Haemorrhoidectomy	Mixed
15	AR	170	280	+	+	+	+	well	Self	Nil	Mixed

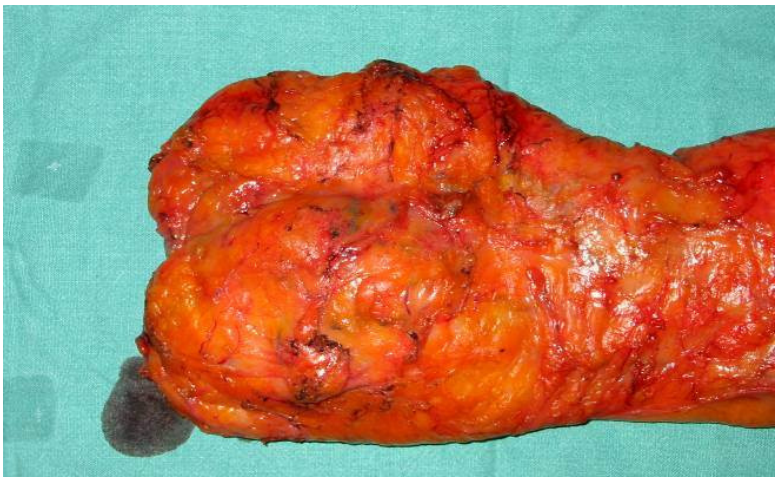
ABDOMINO PERINEAL RESECTION OF RECTUM



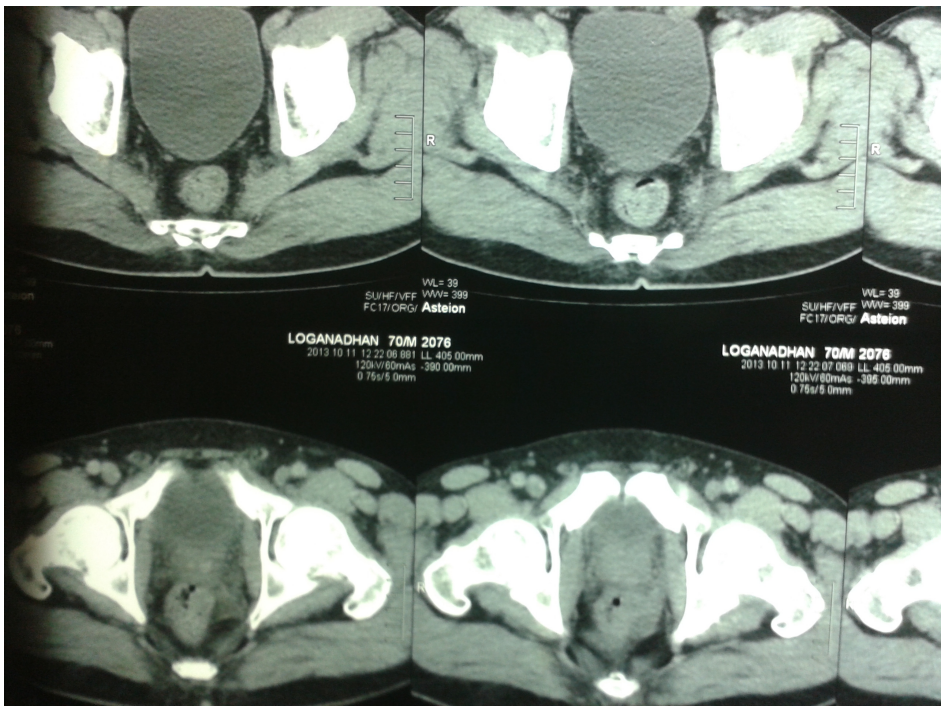
ANTERIOR RESECTION OF RECTUM



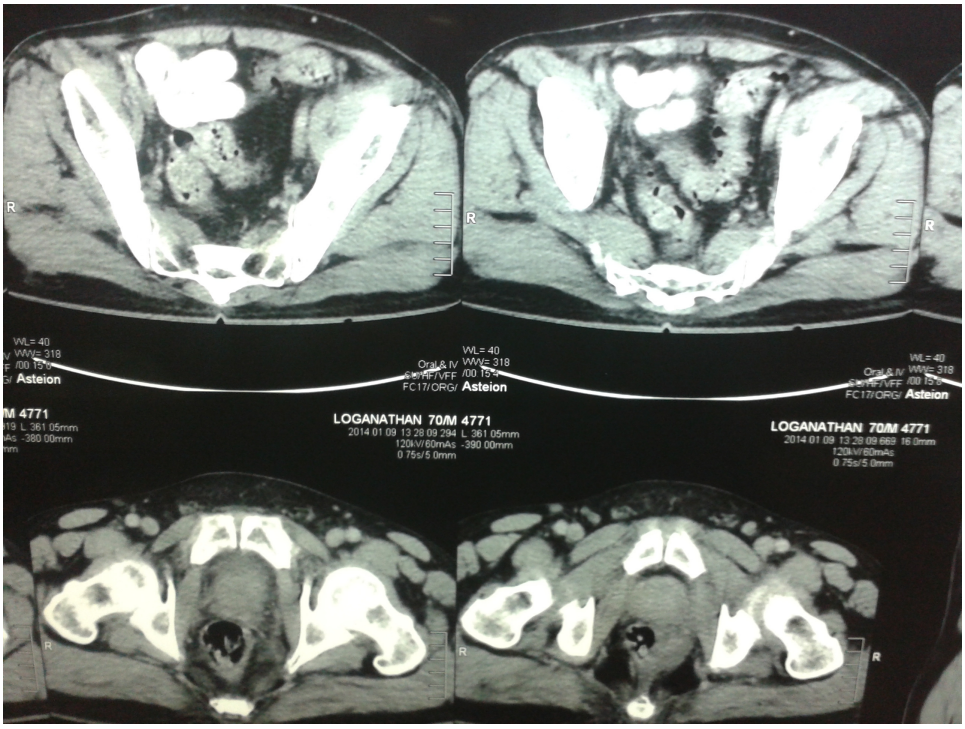
TOTAL MESORECTAL EXCISION



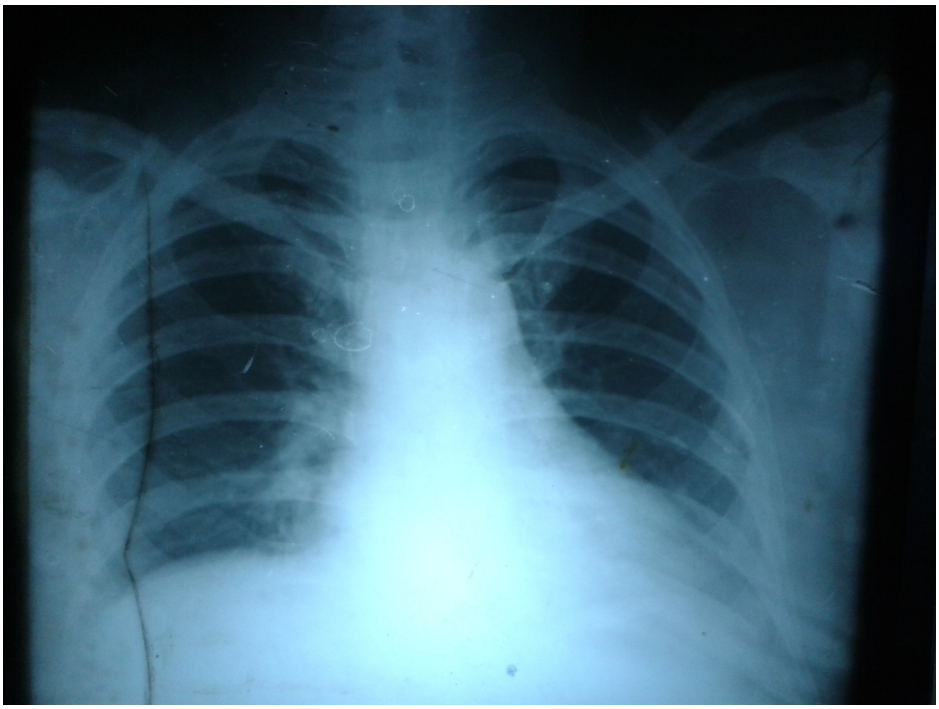
PRE TREATMENT



POST TREATMENT



X-RAY CHEST



RT SIMULATION

Welcome to your new class homepage! From the class homepage you can see all your assignments for your class, view additional assignment information, submit your work, and access feedback for your papers.

Hover on any item in the class homepage for more information.

Class Homepage

This is your class homepage. To submit to an assignment click on the "Submit" button to the right of the assignment name. If the Submit button is grayed out, no submissions can be made to the assignment. If resubmissions are allowed the submit button will read "Resubmit" after you make your first submission to the assignment. To view the paper you have submitted, click the "View" button. Once the assignment's post date has passed, you will also be able to view the feedback left on your paper by clicking the "View" button.

Assignment Inbox: The Tamil Nadu Dr. M.G.R. Medical University

	Info	Dates	Similarity	
Medical	ⓘ	Start 13-Nov-2013 12:50PM Due 15-Apr-2014 11:59PM Post 13-Nov-2013 3:00PM	23%	Resubmit View

turnitin

Digital Receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

The first page of your submissions is displayed below.

Submission author:	MADESWARAN CHINNATHAMBI
Assignment title:	Medical
Submission title:	ANALYSIS OF PRESENTATION, MA..
File name:	1-4-14.docx
File size:	175.56K
Page count:	59
Word count:	8,307
Character count:	47,807
Submission date:	01-Apr-2014 11:32AM
Submission ID:	411459955